REMARKS

I. Status of the claims

Claims 1-3, 6, 7, 10-15, and 21-28 are pending. Claims 4, 5, 8, 9, 16-20, and 24-35 are hereby canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to any canceled subject matter. Claims 24-29 were withdrawn due to Applicants' election of Group II (claims 1-23 and 30-35) and are canceled herewith simply to expedite prosecution. Claims 1, 10, 12, 13, 21, and 22 are amended for the following reasons:

The method of claim 1 is amended so that it is drawn to a method of generating "an IgA antibody response specific for an antigen" at a mucosal surface of "a vertebrate subject in need thereof." Support for this amendment is found in original claim 4. Furthermore, the Examples of the present application teach that mucosal IgA responses are induced after delivery of particulate vaccine compositions into or across the skin. It also is evident from the application as a whole that the particulate vaccine compositions of the presently-claimed invention are intended for the use in generating a mucosal IgA antibody response in a vertebrate subject in need thereof. See page 4, lines 25 to 29 and page 5, lines 4 to 10.

Claim 1 also is amended to indicate that the vaccine composition that is delivered to the vertebrate comprises a nucleic acid that encodes a desired antigen. The antigen may now be "derived or obtained from a pathogen that enters said subject's body via a mucosal surface," as specified in original claim 5.

Applicants have incorporated into claim 1 the subject matter of original claims 9, 19, and 20. Hence, claim 1 is amended to recite a step of "coadministering an adjuvant composition to the vertebrate subject, wherein the adjuvant composition comprises an oligonucleotide containing a CpG motif and an ADP-ribosylating toxin." Likewise, Example 5 of the application discloses coadministration of an adjuvant composition that comprises an oligonucleotide containing a CpG motif and an ADP-ribosylating toxin.

Claims 10, 12, 13, 21, and 22 are amended simply to correct claim dependencies due to Applicants' cancellation of certain claims. Hence, these claims all now refer to claim 1.

Since none of these amendments introduce new matter, Applicants respectfully request their entry and consideration for examination.

II. Priority claim

Applicants have amended the first paragraph at the first page of the specification to appropriately refer to parent application USSN 09/710,104 and its status (abandoned).

III. Claim objections

Claims 1-23 and 30-35 are objected to for reciting a non-elected invention. Applicants have amended claim 1 to adopt the Examiner's suggestion that it recite that the vaccine composition comprises a nucleic acid encoding an antigen. See subsection 3 at page 2 of the office action. Claims 8 and 30-35 are canceled and, therefore, the objection of those claims is moot.

The Examiner requests clarification of the term "into or across the skin" and, in particular, whether "into the skin" means the same as "across the skin." These terms are not equivalent and Applicants direct the Examiner's attention to the passage at page 9, line 25 to page 10, line 5 which discusses transdermal delivery. "Into the skin" means that vaccine particles are delivered into the layers of the skin, e.g., they are delivered into the skin dermis or epidermis layers; while "across the skin" means that particles are delivered through at least a top layer of skin. Hence, the two terms do not mean the same thing. Applicants believe that this explanation should clarify the terms.

IV. Rejection of claims 30-35 under Section 112, first paragraph

Claims 30-35 are rejected under Section 112, first paragraph as allegedly unpatentable because the specification does not allegedly provide enablement for preventing a disease using a nucleic acid particulate vaccine. See subsection 4 at page 3 of the office action.

Purely for the sake of expediting prosecution, Applicants have canceled claims 30-35 and, therefore, this rejection is moot.

V. Neither Burkoth nor Sato anticipates claims 1-7 because neither publication teaches coadministering an nucleic acid-based adjuvant that contains the recited elements

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 98/10750 ("Burkoth"). Claims 1, 3-5, 91-14, and 16-19 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Sato *et al.*, Science, 273, pp. 352-354 ("Sato").

Claim 1 is amended to recite coadminstering an adjuvant composition that comprises (i) an oligonucleotide containing a CpG motif and (ii) an ADP-ribosylating toxin, alongside the particulate vaccine composition. Neither Burkoth nor Sato discloses coadminstration of the recited adjuvant composition. Accordingly, claims 1-7 are not anticipated by either publication. Applicants respectfully request, therefore, that this rejection be withdrawn.

VI. The state of conventional wisdom and immunological dogma just prior to the priority date of the present application was such that no combination of the prior art would have rendered the presently-claimed invention as obvious

The present invention concerns the generation of an IgA response at a mucosal surface of an individual by delivery of a particulate vaccine composition: "the hallmark of a mucosal immune response is the generation of IgA antibodies" (page 12, lines 28 to 29 of the application).

The inventors were the first to recognise, however, that delivery of a particulate vaccine into or across the skin could result in the generation of an IgA response at a mucosal

surface (mucosal immune response). In fact, the conventional wisdom and, indeed, the prevailing immunological dogma at the priority date of the present case, was that (1) the *systemic* and *mucosal* immune systems were quite different to one another and (2) mucosal administration of a vaccine was required to generate mucosal immunity. Hence, Applicants relate in the specification that it "is commonly thought that vaccination by parenteral injection using a syringe and needle does not lead to a mucosal immune response and that mucosal immunity can only be generated by direct application of vaccines to the mucosal tissue" (specification at page 1, lines 16 to 18).

This is also supported by McCluskie and Davis, J. Immunol., 161, pp. 4463-4466, 1998 ("McCluskie"), which states at page 4463, left-hand column, lines 3 to 7 that: "[I]n general parenteral antigen delivery induces only systemic immunity whereas mucosal delivery can trigger both mucosal (i.e., secretory IgA responses) immunity at local and distal sites as well as systemic responses."

In light of this accepted understanding, it would not have been obvious to a person skilled in the art at the time the invention was filed, that delivery of a particulate vaccine composition into or across the skin of a subject would result in an IgA antibody response at a *mucosal* surface of the subject. In contrast, the person skilled in the art would have expected transdermal delivery to induce only *systemic* immunity.

Applicants' unexpected finding, namely that mucosal immunity could be achieved by delivering a vaccine into or across the skin, also confers other advantages. For instance, vaccine administration through the skin is conventional, is technically less demanding than mucosal delivery and has fewer safety concerns than delivery to the more sensitive mucosal surfaces. All of these attributes could not have been envisioned by the skilled person at the time the invention was filed for the reasons conveyed in the preceding passage.

(a) As acknowledged by the Examiner, Burkoth does not teach an adjuvant-vaccine combination using a needleless syringe and therefore claim 15 is not unpatentable

Claim 15 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Burkoth (supra) in view of Kaiserlian *et al.*, European J. Dermatology, 9(3), pp. 169-176, 1999 ("Kaiserlian").

By virtue of its dependency on claim 1, the method of claim 15 requires co-delivery of the claimed adjuvant composition using the recited needleless syringe powder injection device. Hence, even though Burkoth discloses the use of a needleless injection device to effect transdermal delivery of a desired powder, the immunological effect would not have been expected because Burkoth, as the Examiner acknowledges, does not teach any adjuvant in combination with a vaccine. See the Office's position at page 10, lines 8-10 and page 10, lines 15-16.

(b) Claims 20-23 and 30-35 not unpatentable because there was no motivation to combine the cited art and certainly no expectation that such a combination would have created a successful vaccination composition and strategy

Claims 20-23 and 30-35 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Burkoth (supra) in combination with Kaiserlian (supra) and McCluskie and Davis, J. Immunol., 161, pp. 4463-4466, 1998 ("McCluskie"). At the outset, Applicants note that since claims 30-35 are canceled, this rejection applies only to pending claims 20-23.

In order to understand any alleged impact of the combination of the cited art as a whole, Applicants take this opportunity to first relate the allegedly pertinent teachings of each publication separately.

Burkoth discloses particulate vaccine compositions comprising a nucleic acid encoding an antigen which are suitable for delivery into or across the skin of a vertebrate subject.

Kaiserlian discloses the use of oligonucleotides containing a CpG motif as an adjuvant in plasmid (not particulate) DNA vaccines.

McCluskie discloses mucosal vaccine compositions which comprise a combination of an ADP-ribosylating toxin and an oligonucleotide containing a CpG motif and generate an immune response at a mucosal surface (Figure 3 and the first paragraph of Materials and Methods on page 4464). McCluskie also discloses that the two adjuvants act synergistically (first paragraph, left-hand column, page 4464 to fifth paragraph, right-hand column, page 4465 and Figures 1 to 3).

It would not have been obvious for a person skilled in the art to combine the teachings of Burkoth, Kaiserlian, and McCluskie and arrive at the claimed subject matter of the claims. Indeed, he would not have been motivated in any sense by the publications or the general knowledge of the state of the art to even locate and combine these disparate references.

Firstly, it would not have been obvious for a person skilled in the art to deliver a particulate vaccine composition into or across the skin to generate an immune response at a mucosal surface because the conventional wisdom and immunological dogma related in the preceding passage envisioned no such immunological reaction. In fact, McCluskie indicates that a vaccine administered into or across the skin would not result in a mucosal immune response. See page 4463, left-hand column, lines 3 to 7 of McCluskie, which indicates that only systemic immunity results from parenteral antigen delivery.

Secondly, it would not have been obvious for the skilled person at the priority of the present application to combine the teaching of these documents as the Examiner suggest because there would have been no incentive or motivation upon the skilled person to combine Burkoth with Kaiserlian and McCluskie. Indeed, significant modifications of Burkoth method and compositions would have been necessary. For instance, Burkoth discloses the use of *particulate* compositions, whereas Kaiserlian discloses the use of CpG motifs as an adjuvant for *plasmid* vaccine compositions. See page 3 of Kaiserlian ("Adjuvanticity of plasmid DNA: immunostimulatory DNA sequences").

Furthermore, nothing in Kaiserlian or Burkoth suggests that Kaiserlian's CpG motifs may be applied to particulate vaccine compositions. Hence, it would not have been obvious for the skilled person to combine the teaching of Kaiserlian with Burkoth.

In addition, McCluskie discloses *liquid*, not *particulate* vaccine compositions. Nothing in McCluskie or Burkoth suggests that Burkoth's formulation could be modified to accommodate McCluskie's liquid approach. Neither publication suggests that McCluskie applies to particulate vaccine compositions. Hence, it would not have been obvious for the skilled person to combine McCluskie with Burkoth.

Moreover, McCluskie teaches that intranasal, i.e., mucosal, administration of a DNA vaccine generates an immune response at the nasal, i.e. mucosal, surface. See the first paragraph of Materials and Methods on page 4464 and Figure 3. McCluskie does not, however, relate any data for delivery of vaccines or adjuvants via the skin or any other non-mucosal route. In fact, and as noted above, McCluskie indicates that a vaccine administered into or across the skin would not result in a mucosal immune response (page 4463, left-hand column, lines 3 to 7).

As already touched upon, the mucosal and systemic immune systems are quite different and show different responses to vaccination. Hence, an adjuvant that can effectively generate a mucosal immune response when administered at a mucosal surface, as in McCluskie, is not necessarily capable of generating an effective mucosal immune response when given systemically.

Also, given the gross differences in the effects of vaccination via the two routes, it would not have been possible to predict from the results of McCluskie that the combination of CpG motifs and ADP ribosylating enzymes would have a synergistic effect on mucosal immunity when delivered to a distant site, such as the skin. Hence, there would have been no motivation for the skilled person to combine McCluskie and Burkoth. Even if the skilled person would have been so inclined, he would have had no reason to expect that combination

to work. That is, no combination of the cited art would have led the skilled person to believe the resultant composition and method would have been successful.

For at least these reasons, Applicants do not believe that the claimed invention as recited in claims 20-23 (claims 30-35 are canceled) are unpatentable. Accordingly, Applicants respectfully request withdrawal of this rejection.

VII. Conclusion

Applicants believe that these claims are now in condition for allowance. The Examiner is invited to contact the undersigned if it is felt that a telephone interview would expedite any aspect of examination.

Respectfully submitted,

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